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Sodium Percarbonate: A Multifunctional Reagent For The Preparation Of Optically Active 4-Hydroxy-Δ^2-Isoxazolines

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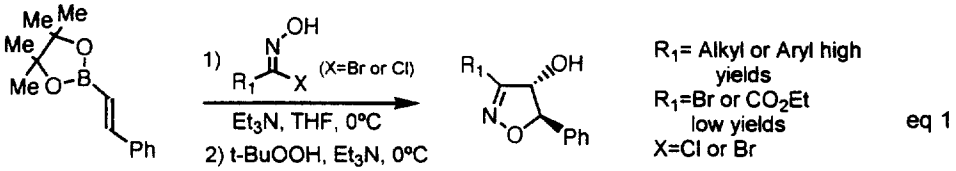
Abstract: In this letter we report a general method for the preparation of optically active 4-hydroxy-Δ^2-isoxazolines. This one-pot method employs sodium percarbonate for nitrile oxide generation, oxidation of the intermediate boronic ester substituted Δ^2-isoxazoline, and cleavage of the chiral auxiliary from the final product. © 1997 Elsevier Science Ltd.

Sodium percarbonate, ($Na_2CO_3 \cdot 1.5H_2O_2$), is a solid compound which is considered to be a "solid form" or "dry carrier" of hydrogen peroxide. Two recent reviews have described some applications of sodium percarbonate in organic synthesis.[3, 4] Due to the presence of sodium carbonate as well as hydrogen peroxide, sodium percarbonate can also serve as a base in addition to being an oxidizing agent. We wish to report the multifunctional use of sodium percarbonate in a one-pot preparation of optically active 4-hydroxy-Δ^2-isoxazolines, which have been shown to be versatile intermediates for the synthesis of amino sugars and a number of other biologically important molecules.[5]

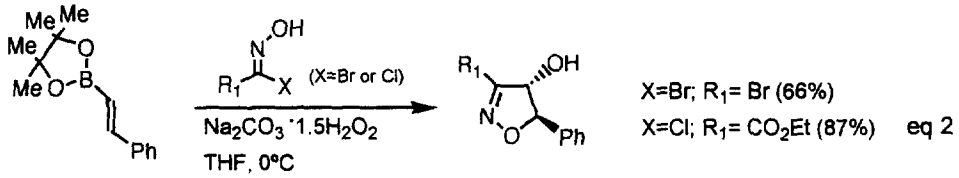
We have previously reported the use of 1,2-disubstituted vinylboronic esters in nitrile oxide cycloadditions followed by immediate oxidation of the cycloadduct to afford 4-hydroxy-Δ^2-isoxazolines.[6] We have also recently reported the extension of this methodology to afford optically active 4-hydroxy-Δ^2-isoxazolines.[7] In our previous studies the yields for 3-alkyl and 3-aryl-substituted-4-hydroxy-Δ^2-isoxazolines were good; however, when an electron deficient nitrile oxide was employed the yields were low (eq 1).



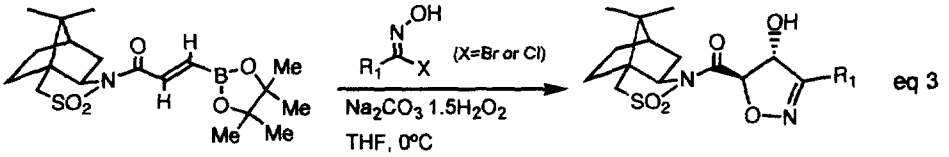
eq 1

We explored a number of variations on the reaction shown above in an effort to improve the yield from the reactions employing electron deficient nitrile oxides. It was believed that part of the problem in these reactions centered around the dimerization of the nitrile oxide to afford the furoxan.[8] After carrying out a

number of experiments, it was found that treating a solution of the vinylboronic ester and hydroximic acid halide with sodium percarbonate was the answer. In these reactions the sodium percarbonate not only served as a base to generate the nitrile oxide but also carried out the oxidation of the intermediate boronic ester substituted Δ^2-isoxazoline to afford the 4-hydroxy-Δ^2-isoxazoline in good yield (eq 2). The low solubility of sodium percarbonate in the reaction mixture allows for the slow generation of the nitrile oxide, this decreases the competing nitrile oxide dimerization. Nitrile oxide cycloadditions carried out under these conditions were found to provide the same very high levels of regioselectivity observed in all previous nitrile oxides cycloadditions with 1,2-disubstituted vinylboronic esters. [6, 7]



After successfully employing sodium percarbonate in the achiral systems, we explored the use of sodium percarbonate in our procedure which affords optically active 4-hydroxy-Δ^2-isoxazolines. [7] These reactions afforded the optically active 4-hydroxy-Δ^2-isoxazolines, which bear an electron withdrawing group in the 3-position, in good yield (eq 3). As reported in previous nitrile oxide cycloadditions employing optically active vinylboronic ester **1** [7], only one diastereomer of the cycloadduct was observed in these reactions. [7]



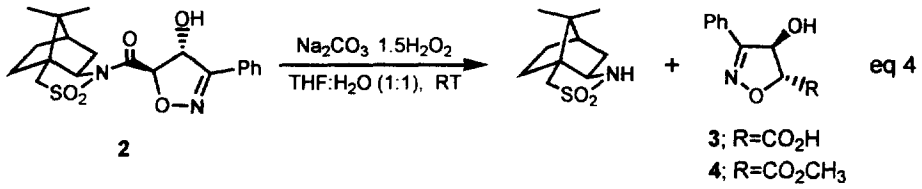
1

R_1= Br (69%)

R_1= CO_2Et (87%)

Further studies have shown that the sodium percarbonate procedure shown above (eq 3) provides the optically active 4-hydroxy-Δ^2-isoxazolines in good yield with both electron deficient and electron rich nitrile oxides. The diastereoselectivities and yields obtained in cycloadditions employing the sodium percarbonate procedure were as high as those obtained with the triethylamine/*t*-BuOOH method previously reported. [7] In the

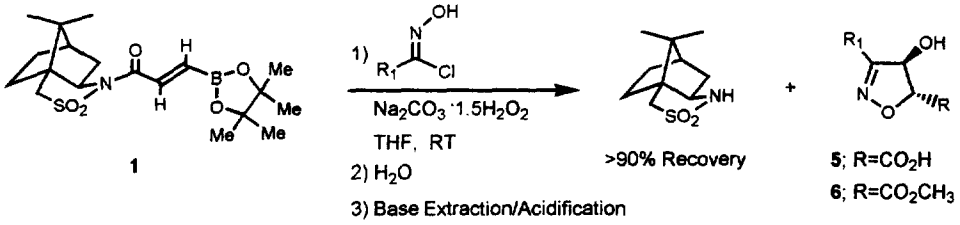
course of carrying out these studies, we found that treatment of the optically active cycloadduct (**2**)[7] with water and sodium percarbonate cleaved the chiral auxiliary to afford the camphorsultam and optically active carboxylic acid substituted 4-hydroxy-Δ^2-isoxazoline (**3**). The carboxylic acid substituted 4-hydroxy-Δ^2-isoxazoline (**3**) could be extracted into aqueous base, and after acidification and extraction, converted into the methyl ester (**4**) with diazomethane. (CAUTION!)



2

3; R=CO_2H
4; R=CO_2CH_3

These results prompted us to explore the possibility of carrying out the cycloaddition/oxidation/auxiliary cleavage in one pot. This proved to be a very efficient method for the preparation of a number of optically active 4-hydroxy-Δ^2-isoxazolines. Treatment of a THF solution of vinylboronic ester (**1**) and the hydroximic acid halide with sodium percarbonate afforded a non-homogeneous reaction mixture. The reaction was monitored by TLC and after the cycloaddition/oxidation was complete, water was added. The reaction was stirred 2 hours at room temperature and quenched with $NaHSO_3$. The pH was adjusted to 10 with NH_4OH and extracted with ether. The basic, aqueous solution was acidified with 1N HCl to afford the carboxylic acid substituted 4-hydroxy-Δ^2-isoxazoline (**5**) which was extracted with ether. The carboxylic acid was converted into the methyl ester (**6**) with diazomethane. The organic layer from the original aqueous base extraction could be evaporated to afford the camphorsultam in >90% yield.

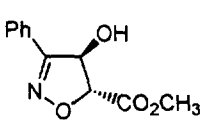


1

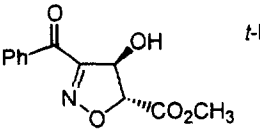
5; R=CO_2H
6; R=CO_2CH_3

A number of optically active 4-hydroxy-Δ^2-isoxazolines have been prepared employing this one-pot procedure. The isolated yields of some of the molecules prepared with this one-step procedure are shown

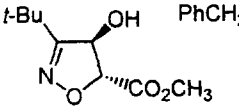
below.[9] Further studies, including the employment of the optically active 4-hydroxy-Δ^2-isoxazolines produced in this work in the synthesis of natural products, are currently underway.



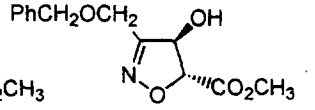
7 (87%)



8 (76%)



9 (80%)



10 (68%)

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References and Footnotes:

1. Present address: Schering-Plough Research Institute, 2015 Galloping Hill Rd., Kenilworth, NJ, 07033.
2. Present address: Armstrong Atlantic State University, Department of Chemistry and Physics, 11935 Abercorn Street, Savannah, GA 31419.
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5. For a summary of the various methods available for the preparation of 4-hydroxy-Δ^2-isoxazolines see: references 3-8 in Wallace, R. H.; Liu, J. *Tetrahedron Lett.* **1994**, *35*, 7493. For methods which yield optically active of 4-hydroxy-Δ^2-isoxazolines see: Wade, P. A.; Shah, S. S.; Govindarajan, L *J. Org. Chem.* **1994**, *59*, 7199. Davis, F. A.; Kumar, A.; Reddy, R. E.; Chen, B.; Wade, P. A.; Shah, S. W. *J. Org. Chem.* **1993**, *58*, 7591. Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898.
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9. All yields shown are isolated yields, and all new compounds gave satisfactory spectroscopic data, (^{1}H NMR, ^{13}C NMR, IR, and HRMS).

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